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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER |
|---|
| LAMBERTSON, DAVID A |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | 14 |

DATE MAILED: 09/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/991,099 | POLLARD ET AL. | |
| | Examiner | Art Unit | |
| | David A. Lambertson | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-8 and 14-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Election/Restrictions*

Claims 1-28 are pending in the instant application.

Claims 1-10 and 14-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12.

Claims 9-13 are ready for examination in the instant application.

### *Priority*

Applicant's claim for domestic priority to US Application 60/252,661 under 35 U.S.C. 119(e) is acknowledged.

### *Information Disclosure Statement*

The information disclosure statement filed June 6, 2003 as Paper No. 11 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Several of the listed references (A1, A2, A5 and A6) were not present with the IDS. These references have been lined through as not being considered. The remaining references have been initialed as considered, and a signed form of the form PTO-1449 is attached to this Office Action.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 9-13 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. The invention is drawn to a method of identifying compounds that modulate the interaction between MSH4 and MSH5 (claims 9 and 10) and a method of identifying a contraceptive compound that modulates the interaction between MSH4 and MSH5 (claims 11-13). Although compounds can potentially be identified by the claimed methods, there is no substantial and/or specific use for the identified compounds. As a result, there can be no substantial and/or specific use for the methods of identifying the compounds.

Applicant asserts throughout the specification that a compound identified as being capable of modulating the interaction between MSH4 and MSH5 can be used either as a contraceptive or as a drug for fertility-related conditions. Specifically, a compound that inhibits the interaction between the MSH4 and MSH5 proteins would theoretically be useful as a contraceptive, and a compound that enhances their interaction would theoretically be useful as a fertility drug. This is based upon the knowledge that: (1) MSH4 and MSH5 are both known to participate in meiotic recombination events that are present during spermatogenesis/oogenesis, (2) that the deletion of either protein alone in a mouse model results in sterility, and (3) that the two proteins are capable of interacting with each other in both a mammalian and a yeast two-hybrid system. However, there is no indication in either the prior art or the instant specification that the interaction between the MSH4 and MSH5 proteins is biologically relevant to either meiotic recombination or an effect on fertility. In fact, there is no indication that disrupting or

enhancing the interaction between MSH4 and MSH5 will have any useful effect at all. For example, if both proteins were expressed (instead of deleted, either individually or in concert, as in the prior art and the instant specification), there is no indication that meiotic recombination would be prevented or that sterility would be induced. This is simply a presumption that is made because both proteins interact and are involved separately in meiotic recombination and fertility. The fact that the proteins have been implicated in meiotic recombination and fertility (by deletion analysis) does not equate to their interaction being relevant to meiotic recombination and fertility. Thus there is no nexus between the interaction of MSH4 and MSH5 and a biological activity, therefore there is not a substantial or specific use for compounds that modulate the interaction between MSH4 and MSH5. Since there is not a substantial or specific use for the compound that is identified, thus there cannot be a substantial or specific utility for the methods of identifying the compounds.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

**Nature of the invention.** The nature of the invention is a method of identifying a compound that is capable of modulating the interaction between MSH4 and MSH5. In some embodiments, the method is directed to identifying a compound that is indicated as being a contraceptive compound, which has the ability to inhibit the interaction between MSH4 and MSH5. In order for the invention to be enabled, the skilled artisan must be able to use the invention; in other words, the skilled artisan must have the ability to productively use a compound identified by the claimed method, otherwise the skilled artisan would not be apprised of what to use the method for.

**State of the art and Level of skill in the art.** The state of the art clearly indicates that the MSH4 and MSH5 proteins are specifically involved in meiotic recombination, and that the disruption of either or both of these proteins results in sterility in a mouse model. This is provided by the demonstration that the deletion of either or both of these genes in a transgenic mouse results in the sterility of the mouse. However, there is no explicit or implicit indication that an interaction between these two proteins is necessary for their roles in meiotic recombination.

The direct interaction of these proteins is questionable, as it is still unclear if there is a bridging molecule between MSH4 and MSH5. In fact, Pochart *et al.* (*J. Biol. Chem.* **272**:30345-30349, 1997; see entire document; henceforth Pochart) demonstrates that MSH4 and MSH5 co-immunoprecipitate and give a positive selection in a two-hybrid system (see for example the Abstract), but also raises the possibility that the interaction is bridged by a third protein (see for example page 30348, right column, last sentence on the page). Significantly, it is also possible that a non-protein molecule, such as DNA, bridges the interaction between the two molecules; this is particularly relevant in this situation, where the two molecules in question are capable of binding to DNA. For instance, it is possible that both molecules bind to a DNA molecule, where they are in proximity to each other, thereby allowing the proteins to be both co-immunoprecipitated and reconstitute the transcription factor necessary to initiate a positive two-hybrid signal. Thus, the skilled artisan cannot predictably ascertain from the prior art that there is indeed a direct interaction between these proteins.

In addition, there is no indication in the prior art that the interaction between MSH4 and MSH5 is even necessary for meiotic recombination. This is especially true in this instance with regard to the fact that there is an unpredictability associated with whether or not MSH4 and MSH5 actually interact in a direct manner. The simple fact that two proteins interact and that are involved in the same functional pathway does not indicate that the interaction is directly related or even relevant to the functional pathway.

For example, van Nocker *et al.* (*Mol. Cell. Biol.* **16**:6020-6028, 1996; see entire document; henceforth van Nocker) identified a proteasome subunit that was capable of physically interacting with multi-ubiquitin chains, called Mcb1 (see for example the Abstract and

Figure 2). Multi-ubiquitin chains are known to be necessary elements for the targeting of substrates to the proteasome for degradation, presumably through a direct interaction with a proteasome subunit such as Mcb1 (see for example page 6021, left column, first full paragraph). Interestingly, a deletion of the Mcb1 proteasome subunit demonstrated a "defective proteolysis" phenotype, consisting of sensitivity to the amino acid analogs L-canavanine and *p*-fluorophenylalanine, and a moderate stabilization of certain types of ubiquitinated substrates (see for example the Abstract, Figure 5, and Figure 8), seemingly confirming a role for Mcb1/multi-ubiquitin chain interaction in proteasome dependent degradation. However, a subsequent paper from the same group (Fu *et al.*, *J. Biol. Chem.* **273**:1970-1981, 1998) identified a specific domain within Mcb1 that was responsible for its interaction with multi-ubiquitin chains (see for example the Abstract, Figure 3). Curiously, this domain was not required for rescuing the phenotypes associated with a deletion of Mcb1 (i.e., the proteolysis phenotypes), seemingly contradicting the connection between the physical interaction of Mcb1 and multi-ubiquitin chains and their respective roles in proteolysis (see for example the Abstract and Figure 5). In this instance, despite the fact that both proteins were implicated in the degradation of proteins, and both proteins interacted (as determined by van Nocker), the interaction was not related to their function in proteolysis (as determined by Fu). Thus, one cannot determine that the interaction between two proteins is necessarily related to their function in the same biological process.

Thus, in the absence of a functional nexus between the interaction of MSH4 and MSH5 and their role in meiotic recombination/fertility, the skilled artisan cannot predict that modulating the interaction between MSH4 and MSH5 will have any affect on meiotic recombination/fertility. As such, there would be no use for a compound that disrupts the

interaction between these two proteins, in effect negating a use for a method of identifying the compound in the first place. Thus, the skilled artisan cannot rely on the teachings of the prior art for guidance on how to use the claimed invention.

**Number of working examples and Guidance provided by applicant.** The instant specification does not remedy the unpredictability set forth in the prior art. There is no further indication in the specification that MSH4 and MSH5 form a direct interaction, as the specification simply reiterates the two-hybrid data that is present in the prior art. Thus it remains unpredictable that such an interaction can be modulated. In addition, there is no guidance or working example in the instant specification that indicates that an interaction between these proteins is even necessary for meiotic recombination to occur. Thus, it is unpredictable that a compound can be identified by the claimed method, where the compound has a real world use as a contraceptive or fertility drug (the asserted utility in the specification). Since these are the only asserted utilities in the instant specification, the skilled artisan cannot be apprised as to how to use the claimed invention. Finally, even if it were indicated that there was a direct relationship between the interaction of MSH4 and MSH5 and their role in meiotic recombination (i.e., that without an interaction between these proteins there is no meiotic recombination), there is no assay provided in the instant specification by which to determine if the identified compound is an effective contraceptive. Thus, the skilled artisan would not be able to identify a "contraceptive compound" specifically, as opposed to a disruptive compound that is insufficient as a contraceptive without further undue and unpredictable trial and error experimentation (e.g., the empirical development of an assay to detect the effectiveness of a compound as a contraceptive).

**Unpredictability of the art and Amount of experimentation required.** The claimed invention is highly unpredictable. First, there is insufficient evidence that a direct interaction occurs between MSH4 and MSH5, therefore it is unpredictable that a method can be performed to modulate an interaction that may not occur. The skilled artisan would have to empirically determine whether or not the interaction actually occurred by designing experiments that negated the possible effects of a bridging molecule such as a third protein or DNA. Second, and perhaps most importantly, it is unpredictable that the interaction between MSH4 and MSH5 is even necessary or relevant to meiotic recombination/fertility. There is no nexus that indicates that modulating the interaction between MSH4 and MSH5 results in the modulation of meiotic recombination/fertility, which is a necessary component for the method to have any enabled real world use. The skilled artisan would first have to determine if the interaction between MSH4 and MSH5 was actually necessary for meiotic recombination to occur prior to being able to use the claimed invention. This would involve a great deal of empirical undue and unpredictable trial and error experimentation, such as generating point mutations/deletions in both MSH4 and MSH5 that were incapable of interacting, and determining the effect of these mutations on meiotic recombination. Finally, the skilled artisan would have to empirically develop an assay to test the effectiveness of an identified compound as a contraceptive. This would also require undue and unpredictable trial and error experimentation.

In conclusion, there are many remaining questions regarding the putative interaction between MSH$ and MSH5, and their roles in meiotic recombination. Because the skilled artisan would be required to ascertain the true nature of the interaction, its relevance to meiotic recombination and fertility, and a means by which to determine the contraceptive effectiveness

of a compound identified by the claimed method, the claimed method simply represents an invitation to further experimentation. As such, the claimed method is not enabled, as the skilled artisan cannot be apprised of how to use the claimed method.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear from the specification how one can "indirectly contact" MSH4 with a test compound. It appears that the compound would either be in contact with MSH4, or not be in contact with MSH4. Because it is unclear what the intermediate between these two options are, the claim is rendered indefinite.

### *Allowable Subject Matter*

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
AU 1636

DAVID GUZO
PRIMARY EXAMINER